Communications to the Editor

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SYNTHESIS OF (±)11-OXACARBACYCLIN

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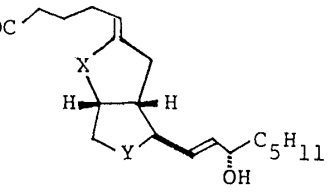
(±)11-Oxacarbacyclin (1) has been synthesized from 4-oxo-cis- and trans-1,2-cyclopentanedicarboxylic acid (3 and 4).

KEYWORDS——prostacyclin analogue; Wittig reaction; carbacyclin analogue; arachidonic acid cascade

Prostacyclin (2a), a very important metabolite of arachidonic acid, has been shown to be a potent inhibitor of human platelet aggregation and a relaxer of certain vascular tissues.[1] The short half life time under physiological conditions limits the clinical use of this compound. Therefore, our research has focussed on the synthesis of orally active and chemically stable analogues of prostacyclin.[2,3] The present paper describes the synthesis of (±)11-oxacarbacyclin (1).



1 11-oxacarbacyclin (X= CH_2, Y= O)
2a prostacyclin (X= O, Y= $CH_{\sim\sim}OH$)
2b carbacyclin (X= CH_2, Y= $CH_{\sim\sim}OH$)

The acid anhydride (5), which was obtained from the cis dicarboxylic acid (3)[4] by heating with Ac_2O at 140°C or the trans dicarboxylic acid (4)[4] by heating with meta-phospholic acid at 200°C, was reduced with $NaBH_4$ in aq.THF to the hydroxy lactone (6) in 78% yield. Subsequent Jones oxidation of 6 afforded the lactone (7) which retains the cis ring junction.

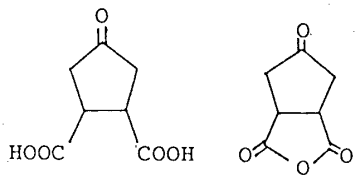
The introduction of the ω-chain was accomplished by an indirect method as follows. Acetalization of 7 by the usual method afforded the acetal (8) in 83% yield as colorless needles, mp 76°C. Reduction of 8 with diisobutylaluminum hydride (DIBAL-H) followed by the Wittig reaction with carbomethoxymethylene-triphenylphosphorane in toluene at 100°C yielded the α,β-unsaturated ester (10) in 76% yield from 8. On heating at 50°C in the presence of K_2CO_3 in MeOH, the primary alcohol in 10 was converted into the tetrahydrofuran ring (11) via

the Michael type addition. Direct conversion of the lactol (9) to 11 was accomplished in good yield by heating with carbomethoxymethylenetriphenylphosphorane in xylene under reflux. Although 11 showed one spot on TLC (AcOEt:hexane 1:2) and each signal of the methyl ester and the acetal in ^{1}H-NMR was observed as a singlet at 3.70 and 3.92, respectively, the aldehyde derived from 11 was observed as two adjacent spots (Rf 0.72 and 0.62 in AcOEt:hexane 1:2) on TLC. This fact suggests that compound 11 consists of a mixture of the $C_{12}\alpha$-methyl ester and the $C_{12}\beta$-methyl ester (PG numbering).

The ester function was converted to the aldehyde by the following route. The methyl ester moiety in 11 was reduced with $LiAlH_4$ in ether to the corresponding alcohol (12), which was converted to the tosylate (13) by the usual method. Treatment of 13 with NaI in HMPA afforded the iodide (14) in 98% yield. The dehydrohalogenation reaction of 14 to the vinyl compound (15) by treatment with t-BuOK in DMSO at room temperature and subsequent Lemieux-Johnson oxidation ($NaIO_4$-OsO_4) afforded a mixture (Rf 0.72 and 0.63 in AcOEt:hexane 1:2) of the $C_{12}\alpha$- and the $C_{12}\beta$-aldehyde. On treatment with K_2CO_3 in MeOH at 50-60°C, a mixture of the C_{12}-epimeric aldehydes was isomerized to the sole compound having Rf 0.72 which was considered to be the thermodynamically more stable $C_{12}\beta$-aldehyde (16).

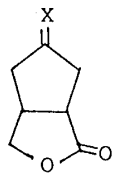
Wittig reaction of 16 with 2-oxo-heptylidenetributylphosphorane in ether at room temperature afforded in 58% yield the enone (17) which on reduction with $NaBH_4$ in MeOH gave a mixture of the C_{15}-epimeric alcohols (18). As attempts to separate them into the $C_{15}\alpha$- and the $C_{15}\beta$-alcohol were unsuccessuful, we were forced to alter the first synthetic plan to separate each alcohol in the last stage of the synthesis. By deacetalization in the usual manner followed by protection of the C_{15}-alcohol with dihydropyran in the presence of p-toluenesulphonic acid, 18 was converted via the compound (19) into the tetrahydropyranyl ether (20) in 98% yield. In order to introduce the α-chain, 20 was subjected to the Wittig reaction with 4-sodiocarboxybutylidenetriphenylphosphorane in DMSO. This Wittig reaction, followed by treatment with CH_2N_2, afforded the ester (21) in a much better yield (98%) than that of the corresponding ketone in carbacyclin (2b) synthesis. The ester (21) could be separated into the 5(E)- and 5(Z)-isomer as follows. The hydrolysis of the tetrahydropyranyl ether in 21 with 3.5% HCl afforded the alcohol (22). By hydrolysis with 5% aq.NaOH and subsequent Jones oxidation, 22 was converted via the compound (23) into the enone which could be separated into the more polar fraction and the less polar fraction by careful column chromatography. The more polar fraction (25) was tentatively assigned to the 5(E)-isomer and the less polar fraction (24) to the 5(Z)-isomer,[5] as in the assignment for carbacyclin (2b) and its 5(Z)-isomer. Reduction[6] of 25 with $NaBH_4$ afforded a mixture of the C_{15}-epimeric alcohols which could be separated into the $C_{15}\alpha$-alcohol (26) and the $C_{15}\beta$-alcohol (27) via the methyl ester. The configuration of the C_{15}-alcohol was tentatively assigned according to a general rule in PG chemistry in which the configuration of the $C_{15}\alpha$-OH was assigned to a more polar fraction on TLC. The hydrolysis of 26 and 27 with 5% aq.NaOH yielded 1[7] and 28, respectively.

11-Oxacarbacyclin(1) inhibited collagen-induced platelet aggregation, but it was appreciably less active (ca. 10^{-2}) than carbacyclin. Details of biological data will be published elsewhere.

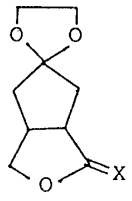


3 cis
4 trans

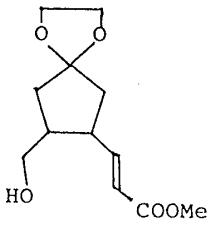
5



6 X= ∼OH
7 X= O



8 X= O
9 X= ∼OH



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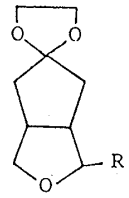
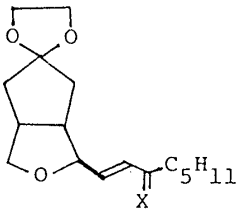
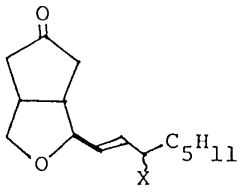


11 R= CH_2COOMe
12 R= ∼OH
13 R= ∼OTs

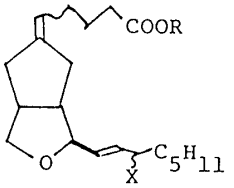
14 R= ∼I
15 R= ∼
16 R= ∼CHO



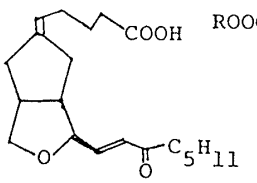
17 X= O
18 X= ∼OH



19 X= ∼OH
20 X= ∼OTHP



21 X= ∼OTHP ; R= Me
22 X= ∼OH ; R= Me
23 X= ∼OH ; R= H



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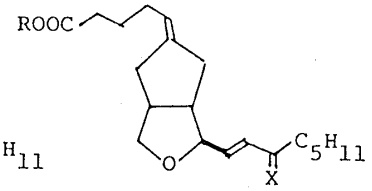

25 X= O ; R=H
26 X= α-OH ; R=Me
27 X= β-OH ; R=Me
28 X= β-OH ; R=H

REFERENCES AND NOTES

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2) K.kojima and K.Sakai, Tetrahedron lett., 1978, 3743.
3) K.Kojima, S.Amemiya, K.Koyama and K.Sakai, Chem. Pharm. Bull., 31, 3755(1983).
4) L.J.Dolby, S.Esfandiari, C.A.Elliger and K.S.Marshall, J. Org. Chem., 36, 1277(1971).
5) The ratio of 5(E) to 5(Z) was 2.2.
6) The C_{15}α-alcohol (26, 250mg), the C_{15}β-alcohol (27, 313mg) and the mixture (26 and 27, 212mg) were obtained from 25 (847mg).
7) Colorless oil. IR(neat):3330, 3360, 1730, 1710, 1125, 1050, 970 cm^{-1}. ^{1}H-NMR($CDCl_3$)δ:0.88(3H,t,J=6Hz,CH_3),3.20-3.50(1H,dd,J=7,4Hz,C_{12}-H), 3.60-3.85(1H,m,C_{15}-H),3.90-4.29(2H,m,C_{10}-2H),5.25(1H,t,J=6Hz,C_5-H), 5.67-5.80(2H,m,C_{13}- and C_{14}-H). MS m/e:336(M^+),318,263,237.

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